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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:	)	
	)	
Inventor: Audrey Goddard et al.	)	
Examiner: Lorraine Spector, Ph.D.	)	
Serial #: 09/202,054	)	Group Art Unit: 1647
	)	
Filed: December 7, 1998	)	Appeal No.: _____
	)	

Title: ANTIBODIES TO HUMAN TOLL HOMOLOGUES

BRIEF OF APPELLANTS

MAIL STOP APPEAL BRIEF - PATENTS
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

In accordance with 37 CFR §41.37, Appellants hereby submit the Appellants' Brief on Appeal from the final rejection in the above-identified application, as set forth in the Office Action dated November 25, 2005.

Please charge the amount of $500 to cover the required fee for filing this Appeal Brief as set forth under 37 CFR §41.37(a)(2) and 37 CFR §41.20(b)(2) to Deposit Account No. 50-0494 of Gates & Cooper LLP. Also, please charge any additional fees or credit any overpayments to Deposit Account No. 50-0494 of Gates & Cooper LLP.

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I. REAL PARTY IN INTEREST

The real party in interest is Genentech, Inc., a Delaware corporation.

II. RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences for the above-referenced patent application.

III. STATUS OF CLAIMS

Claims 28-30, 48-50 and 54-57 are pending in the application.

Claims 28 and 48 have been rejected under 35 U.S.C. §102(b).

Claims 29, 49, 50 and 54 have been rejected under 35 U.S.C. §103(a).

Claims 28-30, 48-50 and 54-57 have been rejected under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph.

The rejections of claims 28-30, 48-50 and 54-57 are being appealed.

IV. STATUS OF AMENDMENTS

No unentered amendments exist.

V. SUMMARY OF CLAIMED SUBJECT MATTER

Briefly, Appellants' invention as recited in independent claims 28, 48 and 55 is directed to antibodies which bind a PRO285 polypeptide sequence. The PRO285 polypeptide is shown in SEQ ID NO: 1 and is encoded by DNA 40021 (SEQ ID NO:2) (see, e.g. Figures 1 and 2 and Example 1 at pages 39-40). Anti-PRO285 antibodies are taught for example at page 5, lines 32-35 and page 32, line 4 - page 37, line 34). Claim 55 recites anti-PRO285 antibodies that are agonist or antagonists of NF-κB activity (see, e.g. page 12, line 38 - page 13, line 25).

VI. ISSUES TO BE REVIEWED ON APPEAL

Claims 28 and 48 stand rejected under 35 U.S.C. §102(b) as being anticipated by Ruggeri et al., WO 91/09614 (Ruggeri).

Claims 29 and 49 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Ruggeri et al., WO 91/09614 (Ruggeri) in view of Coughlin, United States Patent No. 5,256,766 (Coughlin).

Claims 50 and 54 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Ruggeri et al., WO 91/09614 (Ruggeri) in view of Coughlin, United States Patent No. 5,256,766, and further in view of Ladner et al., United States Patent Application No. 4,946,778 (Ladner).

Claims 28-30 and 48-51 stand rejected under 35 U.S.C. §101.

Claims 28-30 and 48-51 stand rejected under 35 U.S.C. §112, first paragraph in view of the rejection under 35 U.S.C. §101.

All of these rejections are being appealed.

VII. ARGUMENTS

A. ARGUMENTS TRAVERSING REJECTION OF CLAIMS 28 AND 48 UNDER 35 U.S.C. §102(b)

Claims 28 and 48 stand rejected under 35 U.S.C. §102(b) as being anticipated by Ruggeri et al., WO 91/09614 (Ruggeri). Ruggeri discloses a 15 residue platelet membrane glycoprotein Ib peptide that includes a 9 amino acid segment that exactly matches a 9 amino acid segment found in the middle of 1049 amino acid PRO285 polypeptide (positions 704-712). The Patent Office asserts that at page 19 and in claim 65 in Ruggeri, antibodies to such peptides are disclosed and claimed. In view of this disclosure, the Patent Office asserts that Appellants claims are anticipated because "one would reasonably expect an antibody raised against Ruggeri's peptide to bind to PRO285" (Office Action dated October 26, 2004). In making this rejection under 35 U.S.C. §102(b), the Patent Office explicitly notes that this is anticipation via inherency and that "[I]t is not necessary that Ruggeri have any knowledge of PRO285 for anticipation to be found" (Office Action dated June 9, 2003, paper #22).

Appellants respectfully traverse the rejection under 35 U.S.C. §102(b) because for example polypeptides such as the 1049 and 806 PRO285 polypeptide sequences recited in claims 28 and 48 do not occur in nature in a 2-dimensional form where every single amino acid residue is exposed at the surface of the molecule and able to interact with other proteins such as antibodies. Instead,

polypeptides are known to fold in three dimensions and the three-dimensional conformation of a polypeptide dictates which antigenic determinants are for example either: (1) exposed at the exterior of the polypeptide and capable of being bound by antibodies; or (2) hidden in the interior of the polypeptide and inaccessible to antibodies.

Because antibody cross-reactivity cannot be predicted in view of factors such as the 3-D conformation of antigenic determinants, the Ruggeri disclosure fails to meet the legal requirements for a finding of anticipation, i.e. that a claim is anticipated only if each and every element set forth in the claim is found in a prior art reference. Specifically, the Ruggeri reference simply fails to provide a disclosure that allows one to determine whether antibodies raised against a 9 amino acid segment within a 15 amino acid platelet membrane glycoprotein Ib peptide having a first 3-D architecture will cross-react with a completely different protein having a second 3-D architecture, for example "a PRO285 polypeptide comprising amino acids 1 to 1049 encoded by SEQ ID NO:2".

In traversing the outstanding rejection, Appellants note that the Patent Office's position that antibodies raised against the 15 amino acid platelet membrane glycoprotein Ib peptide will bind to the 1049 and 806 PRO285 polypeptide sequences recited in the claims is technically uncertain. For example, the 9 amino acid segment in PRO285 that had identity to the 9 amino acid segment in platelet membrane glycoprotein Ib peptide disclosed in Ruggeri occur at positions 704-712, a segment in PRO285 that is flanked on both sides by hundreds of other amino acid residues recited in the claims. These hundreds of flanking PRO285 amino acid residues can assume a three dimensional conformation that physically prevents antibodies raised against the platelet membrane glycoprotein Ib peptide from contacting this segment of 9 amino acids located in the middle of the PRO285 polypeptide. Moreover, a side by side comparison of the residues flanking the identical 9 amino acid segments in these polypeptides shows that while PRO285 has a glutamic acid residue (having a chemically acidic side chain moiety) at position 716 and an arginine residue (having a chemically basic side chain moiety) at position 717, the platelet membrane glycoprotein Ib peptide sequence has two aliphatic leucine residues at the corresponding amino acid positions. These observed differences in the chemical properties of the amino acid side chains that flank the 9 amino acid segments in these different proteins provides evidence that the conformations of the respective antigenic determinants in these molecules are likely to be dissimilar. This difference in the platelet

membrane glycoprotein Ib peptide and PRO285 flanking sequences therefore provides evidence that antibodies generated using the platelet membrane glycoprotein Ib peptide will not cross-react with the PRO285 polypeptides recited in the claims. In view of this, Appellants' attorney speculates that even if the 3-D conformation of PRO285 serendipitously allowed this 9 amino acid segment of the polypeptide to somehow be accessible to an antibody as disclosed in Ruggeri (which is doubtful), it would be more likely than not that the polar chemical properties of the glutamic acid and arginine side chains at positions 716 and 717 in PRO285 would in fact repel any and all antibodies generated against the correspondingly more non-polar chemical properties of the antigenic determinants on the platelet membrane glycoprotein Ib peptide. This is however only a conjecture by the Appellants' attorney because the disclosure in Ruggeri is simply not sufficient to allow one to determine if this does in fact occur.

Setting these technical issues aside however, Appellants' respectfully note that the Patent Office's position that the disclosure in Ruggeri is sufficient to destroy the novelty of Appellants' claims is contrary to case law. In particular, while the Patent Office asserts that the Ruggeri disclosure anticipates the claimed invention via inherency because "it would be more likely than not" that an antibody raised against Ruggeri's peptide will also bind to PRO285 (Office Action dated November 25, 2005), Appellants respectfully note that the Patent Office's conjecture as to what an antibody raised against Ruggeri's 15 amino acid peptide will or will not do is an improper basis for a finding of anticipation. Specifically, courts find that "anticipation of a claimed product cannot be predicated on mere conjecture as to the characteristics of a prior art product". See, e.g. *Ex parte* Standish, 10 USPQ2d 1454, 1457 (Bd. Pat. App. & Int'f 1989). Instead, courts find that a claim is anticipated only if each and every element set forth in the claim is found in a prior art reference. See, e.g. *Verdegaal Bros. V. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

The prohibition on using conjecture as a basis for a finding of anticipation is further articulated in the case law pertaining to anticipation via inherency. In particular, when articulating the legal requirements for a finding of anticipation via inherency, courts state that inherency "may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." See, e.g. M.P.E.P. 2112 and *Continental Can Co. v. Monsanto Co.*, 20 USPQ 2d 1746, 1749 (Fed. Cir. 1991). Instead, to establish inherency, the

extrinsic evidence "must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *Continental Can Co.*, 20 USPQ 2d 1749.

The Patent Office's statement that antibody cross-reactivity "would be more likely than not" demonstrates that the Patent Office's anticipation rejection is based upon conjecture and that the disclosure in WO 91/09614 is not sufficient to allow one of skill in the art to determine whether the antibody cross-reactivity required for a finding of anticipation is necessarily present. Consequently, the disclosure in WO 91/09614 fails to meet the legal requirements for a finding of anticipation via inherency. For this reason, Appellants respectfully request a withdrawal of the rejection under 35 U.S.C. §102(b).

B. ARGUMENTS TRAVERSING REJECTION OF CLAIMS 29, 49, 50 AND 54 UNDER 35 U.S.C. §103(a).

The 35 U.S.C. §103(a) rejections of claims 29 and 49 as being unpatentable over Ruggeri in view of Coughlin, as well as the 35 U.S.C. §103(a) rejections of claims 50 and 54 as being unpatentable over Ruggeri in view of Coughlin and further in view of Ladner rely upon the Ruggeri disclosure as teaching an antibody that binds a PRO285 polypeptide. As noted above, the rejection under 35 U.S.C. §102(b) is not proper because the Ruggeri disclosure fails to disclose an antibody that binds a PRO285 polypeptide. The Coughlin and Ladner disclosures fail to remedy this deficiency. Consequently these references cannot be combined in a manner that renders the subject matter recited in claims 29, 49, 50 or 54 obvious. For this reason, Appellants respectfully request a withdrawal of the rejection under 35 U.S.C. §103(a).

C. ARGUMENTS TRAVERSING REJECTION OF CLAIMS 28-30, 48-50 AND 54-57 UNDER 35 U.S.C. §101

Claims 28-30 and 48-51 stand rejected under 35 U.S.C. §101. Appellants traverse this rejection because Patent Office is requiring Appellants to meet a standard of proof for utility that is contrary to case law as well as the utility the guidelines promulgated by the Patent Office.

Appellants assert that the claimed invention is useful for particular purposes and that these assertions would be considered credible by a person of ordinary skill in the art. During prosecution Appellants provided complimentary evidence to support the asserted utility including the specification disclosure, common knowledge in the art as well as a Declaration from an expert witness. In challenging Appellants' disclosure and expert testimony during prosecution, the Patent Office adopted a standard of proof that it is contrary to case law holding that statements of utility are presumed to be true and that to overcome the presumption of truth that the application enjoys, Office personnel must establish that it is more likely than not that one of ordinary skill in the art would doubt (i.e. "question") the truth of the statement of utility. See, e.g. *In re Langer*, 183 USPQ 288 (CCPA 1974) and *In re Oetiker*, 24 USPQ2d 1443 (Fed. Cir. 1992). As discussed below, the Patent Office's analysis fails to prove that the totality of facts and reasoning suggest that it is more likely that not that the statement of the applicant is false. A summary of Appellants statements and evidence supporting the utility of the claimed subject matter is as follows.

Appellants' disclosure relating to the utility of the claimed subject matter teaches that comparative homology analyses and functional data from Toll family members indicate that PRO285 polypeptide signaling activates NF-κB, an event which leads to the expression of the inflammatory cytokines IL-1, IL-6 and IL-8. See, e.g. page 13, lines 13-25. Appellants' disclosure further teaches that antibodies to the PRO285 polypeptide can act as agonists or antagonists of NF-κB signaling and can therefore be used in methods designed to modulate the expression of genes controlled by NF-κB. See, e.g. page 13, lines 6-25. The specification further teaches that antagonistic anti-PRO285 antibodies may be used in pathologies characterized by an overexpression of IL-1, IL-6 and IL-8 such as septic shock. See, e.g., page 37, lines 10-29. In addition, it is known in the art, methods designed to modulate the expression of IL-1, IL-6 and IL-8 (e.g. via NF-κB activation) can be used in a variety of other contexts in addition to septic shock. For example, reagents which induce the expression of IL-1, IL-6 and IL-8 are used in the topical treatment of warts[1]. Consequently, the utility of the claimed anti-PRO285 antibodies is based for example upon the Appellants' understanding that PRO285 polypeptide signaling modulates NF-κB activity and

that antibodies specific for this receptor can modulate this activity. In this context, the claimed subject matter has a credible, specific and substantial utility because the modulation of NF-κB modulates the expression of the inflammatory cytokines IL-1, IL-6 and IL-8; and pathologies such as septic shock and warts are treated via the modulation of IL-1, IL-6 and IL-8 expression.

The use of an antibody to modulate the signaling of a receptor whose biological activity is associated with a pathological syndrome conforms to established scientific principles and is the principle upon which a significant number of therapeutic regimens are based. In the instant case, the association of PRO285 with NF-κB signaling via homology analyses is an art accepted method known to identify a function associated with a specific amino acid sequences. The use of agonistic and antagonistic antibodies as reagents to modulate the biological activities of a target receptor (e.g. NF-κB signaling) is also well known and accepted practice in the art. It is also known in the art that NF-κB controls the expression of IL-1, IL-6 and IL-8, cytokines whose aberrant expression is observed in a number of pathological syndromes including septic shock. Because the utility asserted by the Appellants is based upon established scientific principles, one of skill in the art would not, as the Patent Office asserts, be considered "false" by a person of ordinary skill in the art. To illustrate this, Appellants provided an opinion of a qualified expert[2] stating that one of skill in the art would find credible Appellants teaching that PRO285 can induce the expression of that IL-1, IL-6 and IL-8 (NF-κB-controlled genes) and that antibodies to PRO285 can be made and used in accordance with routine techniques to modulate the expression of these inflammatory cytokines. For these reasons, Appellants' asserted utility for the claimed subject matter: (1) is readily understood by a skilled artisan; (2) conforms to scientific principles; and (3) is acknowledged in opinion from a qualified expert.

Applicants enjoy a presumption that an asserted utility is true. In order to overcome this presumption of truth that an applicant enjoys, Office personnel must provide evidence sufficient to show that the statement of asserted utility would be considered "false' by a person of ordinary skill in the art. The evidence provided by the Patent Office fails to meet this burden. For example, one

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[1] See evidence appendix for Beutner et al., Am. J. Med. 102 (5A) 28-37 (1997), a copy of which was originally provided as Attachment B with Appellants amendment under 37 C.F.R. §1.116 that was submitted on July 15, 2004.
[2] See evidence appendix for a copy of the declaration under 37 C.F.R. 1.132 by J Fernado Bazan.

of skill in the art would not, as the Patent Office Asserts, disregard the expert opinion regarding the significance of Appellants' homology analysis because "of the six essential residues for IL-R1 signaling domain, only two are conserved in PRO285" (Office Action dated March 15, 2004). Instead, one of skill in the art would note that while only 2 of the six essential residues are identical, homology analysis in this art are not limited to comparisons of identical amino acid residues but also include comparisons of amino acids having conserved (i.e. chemically similar) side chain properties (see Amendment filed by Appellant December 9, 2003 and pages 5-6 of the Amendment filed by Appellant on July 15, 2004). Similarly, because it is known in the art that NF-κB controls the expression of IL-1, IL-6 and IL-8, cytokines whose aberrant expression is observed in a pathological syndromes including septic shock, Appellants provide a reasonable correlation between the activity and the asserted use. Consequently, no further correlation is required (e.g. as asserted in the Office Action dated November 25, 2005).

As noted in M.P.E.P. §2107.02, where an applicant has specifically asserted that an invention has a particular utility, that assertion cannot simply be dismissed by Office personnel as being "wrong" even when there may be reason to believe that an assertion is not entirely accurate. Instead, an assertion of utility is to be considered credible unless (A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based is inconsistent with the logic underlying the assertion. As noted above, neither situation occurs in Appellants' asserted utility. In addition, the Patent Office fails to provide evidence sufficient to show that the statement of asserted utility would be considered "false' by a person of ordinary skill in the art. For example, one of skill in the art would not disregard Appellants' expert testimony in favor of the alternative homology analysis presented by the U.S. Patent Office because this alternative homology analysis excludes amino acid residues having side chains with very similar but not identical chemical properties (which is contrary to art accepted practices in homology analyses). Consequently, the legal presumption that Appellants statement of utility is true has not been overcome by the various arguments presented by the Patent Office. For these reasons, based upon the claims and the asserted utility, there are clear errors in the Patent Office's rejection and further, the rejections fail to establish the elements needed for a prima facie rejection under 35 U.S.C. §101.

D. ARGUMENTS TRAVERSING REJECTION OF CLAIMS 28-30, 48-50 AND 54-57 UNDER 35 U.S.C. §112, FIRST PARAGRAPH

In accordance with M.P.E.P. 2164.07, with the 35 U.S.C. §101 rejection, the Patent Office correspondingly asserts that because the claimed invention is not supported by either a specific, substantial and credible asserted utility, one skilled in the art clearly would not know how to use the claimed invention, and therefore this invention is not enabled (resulting in a rejection under 35 U.S.C. §112, first paragraph).

This rejection is inconsistent with case law and PTO guidelines for making such rejections because, for example, the Examiner provides no evidence to show that one of ordinary skill in the art would reasonably doubt the asserted utility. M.P.E.P. §2164.07 notes that Office personnel should not impose a 35 U.S.C. 112, first paragraph, rejection grounded on a "lack of utility" basis unless a 35 U.S.C. 101 rejection is proper. In this context, a factual showing must be provided if a 35 U.S.C. 112, first paragraph, rejection is to be imposed on "lack of utility" grounds. Specifically, M.P.E.P. §2164.07 states that only after the examiner has provided evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant. As noted above, in the instant case, the Patent Office fails to provide evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility.

In assessing of the credibility of a disclosure, Applicants further note that Section 112 does not require that a specification convince persons skilled in the art that every aspect of a disclosure is indisputably correct. Instead, Section 112 requires that, viewing the evidence as a whole, one skilled in the art would believe that the claimed invention can be made and used with a reasonable expectation of success (see, e.g. *In re Robins*, 166 USPQ 552, 556, CCPA 1970). This standard is reiterated in the guidelines promulgated by the Patent Office for the examination of applications for compliance with the utility requirement of 35 USC 101 and 35 USC 112, first paragraph (see, e.g. 60 Fed. Reg. 36263-02). In particular, cite the portion of section 2(a) of these guidelines which is reproduced below:

> If the applicant has asserted that the claimed invention is useful for any particular purpose (i.e. a 'specific utility') and that assertion would be considered credible by a person of ordinary skill in the art, **do not impose a rejection based on lack of utility.** Credibility is to be assessed from the perspective of one of ordinary skill in the art in view of any evidence of record (e.g. data, statements, opinions, references etc.) that is relevant to the applicant's assertions.

As noted above, Appellants applicant have asserted that the claimed invention is useful for a particular purpose and the Patent Office has failed to met its burden of providing evidence sufficient to show that the statement of asserted utility would be considered "false" by a person of ordinary skill in the art. Instead, as shown for example by the declaration under 37 C.F.R. 1.132 that was submitted with the office action response on December 9, 2003, one skilled in the art would not doubt the asserted utility and would instead know how to use the claimed invention without undue experimentation. For these reasons, there are clear errors in the Patent Office's enablement rejection, one predicated upon a lack of utility. For this reason, Appellants respectfully request a withdrawal of the rejection under 35 U.S.C. §112.

E. CONCLUSION

In light of the above arguments, Appellants respectfully submit that the rejections under 35 U.S.C. §102(b) and 35 U.S.C. §103(a) are in error because the references cited by the Patent Office neither anticipate nor render obvious the claimed invention. In addition, Appellants respectfully submit that the rejections under 35 U.S.C. §101 and 35 U.S.C. §112 are in error because the Patent Office fails to provide evidence sufficient to show that the statement of asserted utility would be considered "false' by a person of ordinary skill in the art. As a result, a decision by the Board of Patent Appeals and Interferences reversing these rejections and directing allowance of the pending claims in the subject application is respectfully solicited.

Respectfully submitted,

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WJW/

CLAIMS APPENDIX

1-27. CANCELLED

28. An antibody which specifically binds to a polypeptide encoded by DNA 40021 (SEQ ID NO:2).

29. The antibody of claim 28 wherein said antibody is a monoclonal antibody.

30. The antibody of claim 29 which blocks the recognition of a Gram-negative or Gram-positive organism by said polypeptide.

31-47. CANCELLED

48. An isolated antibody which specifically binds to a PRO285 polypeptide consisting of amino acid residues 30 to 836 of Fig. 1 (SEQ ID NO:1).

49. The antibody of claim 48 which is a monoclonal antibody.

50. The antibody of claim 49 which is a chimeric, humanized or human antibody.

51-53. CANCELLED

54. The antibody of claim 28 which is a chimeric, humanized or human antibody.

55. An isolated antibody which binds to a PRO285 polypeptide comprising:
(a) amino acids 1 to 1049 encoded by SEQ ID NO:2, or
(b) amino acid residues 20 to 836 of SEQ ID NO:1;
wherein the antibody is an agonist or an antagonist of NF-κB activation.

56. The antibody of claim 55, wherein the antibody is an agonist of NF-κB activation.

57. The antibody of claim 55, wherein the antibody is an antagonist of NF-κB activation.

EVIDENCE APPENDIX

This evidence appendix includes: (1) a copy of Beutner et al., Am J Med. 1997;102(5A):28-37, entered in the record by the examiner as shown by comments and analyses provided in the Office Action of September 10, 2005 (page 4, top paragraph); and (2) a Declaration under 37 C.F.R. 1.132 and two associated attachments, entered in the record by the examiner as shown by comments and analyses provided in the Office Action of October 26, 2004 (page 2, middle paragtaph).

Therapeutic Approaches to Genital Warts

Karl R. Beutner, MD, PhD, *San Francisco, California*, Alex Ferenczy, MD, *Montreal, Quebec, Canada*

Although many treatments are available for genital warts caused by human papillomavirus (HPV), none are uniformly successful in the treatment of this disease. Most current treatment options work by destroying affected tissue, either by a cytotoxic or a physically ablative mode of action. Interferons have antiviral, antiproliferative, and immunomodulatory activities, but these have not translated into a high level of cure rates against warts. With all current treatments, recurrent warts are common. Therapies currently being investigated include a 5-fluorouracil/epinephrine collagen gel that achieves high concentrations of 5-fluorouracil at the site of injection. Other new treatment modalities focus on activating the host's immune system or improving the delivery of therapeutic compounds to the affected site. Imiquimod, a novel immune-response modifier, induces interferon and a number of other endogenous cytokines. A cream formulation containing 5% imiquimod resulted in good total clearance rates and generally tolerable side effects in controlled clinical trials of patients with external genital warts. Perhaps the most effective means for managing HPV disease would be a vaccine that prevents the occurrence of genital warts. Although it is unlikely that such a vaccine will be introduced in the near future, preliminary studies indicate that it may be possible to develop suitable prophylactic and therapeutic vaccines. *Am J Med.* **1997;102(5A):28–37.**

From the Department of Dermatology, University of California at San Francisco, San Francisco, California; and the Departments of Pathology and Obstetrics and Gynecology, McGill University, Montreal, Quebec, Canada.

Requests for reprints should be addressed to Karl R. Beutner, MD, PhD, Solano Dermatology, 127 Hospital Drive, Vallejo, CA 94585.

There are no simple, routinely effective therapies available for the treatment of genital warts, a disease caused by human papillomavirus (HPV). The lack of such therapy often makes the treatment of genital warts a frustrating experience for both the patient and the clinician.

For many diseases, there is little question as to whether offering treatment to a patient is appropriate. Therapy for genital warts is more problematic, however, as some of the recognized goals for treating bacterial sexually transmitted diseases are not necessarily accomplished by treatment of genital warts.[1] Current therapies have a low effectiveness in preventing wart recurrence, and there is little evidence that treatment reduces the likelihood of disease transmission. In many cases, the best that can be hoped for is a temporary reduction of symptoms.

Nevertheless, because genital HPV infections are cosmetically unacceptable and may be associated with discomfort and physical and psychosocial dysfunction, treatment is generally offered to all patients with genital lesions. Other rationales for treatment include the amelioration of symptoms, particularly during wart-free periods, and the possibility of decreased infectivity, not only of HPV, but of other blood-borne infections whose transmission may be enhanced by friable genital warts. Furthermore, in very rare instances, HPV types normally found in genital warts are capable of producing verrucous squamous cell carcinoma (e.g., giant condylomata of Buschke-Löwenstein).

Although experience indicates that most of the current therapies eventually remove warts, recurrences are common. Recurrent warts may be caused by activation of latent virus present in normal skin adjacent to the lesions.[2] New therapies are attempting to improve the efficacy of current treatments by stimulating the host's immune system to eradicate viral infection or by enhancing delivery of therapeutic compounds to HPV-associated lesions.

This article reviews the treatment options available for patients with genital warts, with a focus on new therapies for this disease. These investigational therapies may soon expand the options currently available for the treatment of genital warts.

CURRENT THERAPIES FOR GENITAL WARTS

Many of the therapies used to treat genital warts have been available for decades. In many cases, the

  0002-9343/97/$17.00

TABLE I

Summary of Selected Published Data on Cytotoxic and Physically Ablative Therapies for Human Papillomavirus Infection

Treatment	Average No. of Treatments (range)*	Success Rates (range)*	Recurrence Rates (range)*	References
Cytotoxic agents				
Trichloroacetic acid (Tri-Chlor)	4.0	64–81%	36%	[3, 4]
Podophyllin (Pod-Ben-25, Podocon-25, Podofin)	3.4–6.7	38–79%	21–65%	[7–14]
Podofilox (Condylox)	3.2 treatment cycles (patient applied)	68–88%	16–34%	[12, 14, 18, 19]
5-FU (Efudex, Fluoroplex)	2–2.5 treatment cycles (patient applied)	68–97%	0–8%	[20, 21]
Physically ablative therapies				
Cryotherapy	2.6–3.2	70–96%	25–39%	[3, 4, 7, 11, 26]
CO_2 laser	1.0–2.0	72–97%	6–49%	[21, 28–31]
Electrodesiccation	1.3	94%	25%	[11]
LEEP	NR	72%	51%	[31]
Surgical excision	1.1	89–93%	19–22%	[10, 13]

5-FU = 5-fluorouracil; LEEP = loop electrosurgical excisional procedure; NR = not reported.
*Ranges are reported where possible; not all papers reported data on all of the parameters included in this table.

safety and effectiveness of these treatments have not been assessed in well-controlled, prospective clinical trials. Comparative trials of therapies are also relatively rare. The dearth of such information can make it difficult to evaluate the efficacy of different treatment modalities.

Table I summarizes selected published data on current genital wart therapies. It should be noted that a number of factors can influence the figures presented in this table. In particular, the location and extent of genital warts, the sex of the patients studied, the treatment regimen, and the quality of care can all be important factors in the success of therapy. Both success and recurrence rates are also heavily affected by the time of assessment; in studies with low recurrence rates, patients may simply have been examined for a shorter time period than in studies with high recurrence rates. All of these factors should be kept in mind when evaluating different studies and therapies.

Cytotoxic Agents

Cytotoxic therapies eliminate genital warts by destroying the affected tissue, either through chemodestructive or antiproliferative modes of action. The therapies described in this section are all applied topically. Unlike surgical procedures, cytotoxic therapies do not generally require local anesthesia. Nevertheless, cytotoxic agents are not painless; local skin reactions are common and in some cases can be severe. The relative merits of various cytotoxic agents are shown in Table I.

Trichloroacetic Acid

Trichloroacetic acid (TCA; trade name, Tri-Chlor) is a chemodestructive agent that causes chemical coagulation of genital warts. An 80–90% solution of TCA is applied directly to the genital wart in the clinic or the physician's office. This treatment can be repeated weekly if necessary. Although TCA has little systemic toxicity, lack of control over the depth of penetration and breadth of the treatment area may result in discomfort and, in rare cases, ulcers and scarring.[3] TCA is effective in the initial destruction of external genital warts and works best when used to treat small, moist warts. As TCA is not absorbed in the general circulation, this compound can be used to treat pregnant patients. However, early recurrences may be frequent. In one study, 36% of treated patients had new lesions within 2 months.[4]

Podophyllin

Podophyllin, a plant compound that causes tissue necrosis by arresting cells in mitosis, is frequently used in the treatment of external genital warts. Podophyllin is applied to warts at concentrations of 10–25% in compound tincture of benzoin. After 1–4 hours, the compound should be thoroughly washed off. Podophyllin is usually applied once weekly for up to 6 weeks.

Current recommendations advise that podophyllin application be limited to <0.5 mL or <10 cm^2 per session to decrease the potential for systemic effects, including bone marrow depression. The systemic toxicity of podophyllin precludes its use during pregnancy.[5] In addition, recent studies have indicated that podophyllin resin may contain mutagenic substances.[6] Podophyllin treatment causes local skin reactions, including redness, tenderness, itching, burning, pain, and swelling.

Approximately 50% of patients respond to treatment, but warts recur in about 40% of them.[7–14] Be-

cause podophyllin is not a standardized compound, the efficacy of different batches may vary significantly.[15,16] In addition, podophyllin is ineffective on relatively dry anogenital areas, including the penile shaft, scrotum, and labia majora.[16]

Podofilox

Podofilox (also known as podophyllotoxin), the major biologically active lignan of podophyllin resin, is available by prescription as a 0.5% solution for self-application to external genital warts. Treatment of genital warts with podofilox solution involves twice-daily application with a cotton swab for 3 days, followed by 4 days without treatment. This cycle can be repeated 4–6 times as necessary. It is recommended that treatment with podofilox be limited to a wart area of ≤ 10 cm^2. Pregnant women should not use podofilox.[5]

Podofilox has several advantages over podophyllin, including a standardized formulation and self-administration by the patient. In addition, podofilox has a lower degree of systemic absorption than podophyllin.[17] Comparative studies indicate that podofilox is more effective and results in faster resolution of warts than podophyllin.[12,14] However, as with podophyllin, recurrent warts are common following podofilox treatment. Recurrences occur in approximately one third of previously resolved warts during the first month after treatment.[18,19]

5-Fluorouracil

The antimetabolite 5-fluorouracil (5-FU) inhibits cell growth by interfering with DNA and RNA synthesis. Topical treatment with 5% 5-FU cream can be helpful in the treatment of some forms of genital warts. In the small studies that have been conducted, about 75% of patients experienced clearance of warts; recurrence rates of <10% have been reported.[20,21]

Although topical treatment with 5-FU does not appear to result in significant systemic toxicity,[20] because it is a teratogen its use is contraindicated during pregnancy. The major drawback of 5-FU therapy is a high level of local irritation. Because of this effect, some patients are unable to tolerate treatment.[22] Vaginal ulcerations and one report of vaginal adenosis with clear cell carcinoma have prompted some clinicians to avoid using 5-FU for the treatment of vaginal condylomata.[23,24] However, this agent may be useful for the treatment of vulvar, perianal, penile, and meatal warts. A thin layer of cream is usually spread over freshly cleaned lesions 1–3 times per week. Depending on the sensitivity of the location, the cream should be washed off after 3–10 hours. Applications may continue for several weeks as needed. Because of the possibility of periconceptual fetal toxicity, the patient should be protected from pregnancy, preferably by oral contraceptives, during 5-FU therapy.[25]

Physically Ablative Therapies

There are a number of physically ablative procedures that have been used to destroy genital warts. Although these techniques often achieve reasonable initial success rates, recurrence rates can also be high (Table I). In addition, physically ablative therapies are painful, and anesthesia is usually required.

Cryotherapy

Cryotherapy, usually with liquid nitrogen as the cryogen, can be used to treat genital and anal warts in patients who do not have extensive disease. Cryotherapy results in the freezing and destruction of the wart and a small area of surrounding tissue.

Cryotherapy clears warts in approximately 75% of patients.[3,4,7,11,26] One comparative study found that cryotherapy was more effective than podophyllin in the treatment of condylomata acuminata, resulting in the elimination of genital warts in 79% of patients treated with cryotherapy, compared with 51% in the podophyllin-treated group. At 6 weeks' follow-up, warts recurred in 21% (30/144) of patients.[7]

In cryotherapy, a cryoprobe, modified Q-tip, or fine spray is used to apply liquid nitrogen to the wart. Freezing is usually continued until a frozen area slightly larger (1–2 mm) than the diameter of the wart is formed. This procedure can be repeated at 1- or 2-week intervals; typically, only two or three sessions are required.

Cryotherapy can be painful, but this effect can usually be managed by the use of a local anesthetic. Because there are no systemic effects, cryotherapy can be used to treat genital warts in pregnant women.[27]

Laser Therapy

Properly performed CO_2 laser treatment has achieved excellent results in the treatment of genital warts.[21,28–31] Recurrence rates vary from low (6–17%)[21,23–30] to high (49%).[31] Laser therapy has been successful in the treatment of penile, anorectal, and urethral warts in men[30] and flat warts of the vagina in women.[21] Laser treatment is also a popular choice for the treatment of lesions that have not responded to other therapies and for extensive HPV disease, because the precision of this technique allows normal adjacent tissue to be spared. As with cryotherapy, there are no systemic effects with laser therapy, so it may be safely performed during pregnancy.[32]

The major drawbacks of laser therapy are the special training and expensive equipment required for treatment. Anti-infective measures must be closely

followed during laser therapy. It is essential that a fume evacuator be used to prevent the inhalation of allergens and HPV DNA found in laser plumes.[33] It is not yet known whether HPV DNA spread by laser energy onto treatment fields and the surrounding normal tissue causes recurrent disease.[34]

Because the procedure is associated with extreme heat, local or general anesthesia is required for laser treatment. In unskilled hands, severe thermal damage to underlying tissue can occur. Side effects include pain, itching, and swelling.

Electrosurgery

Electrosurgical methods use high frequency current to destroy (fulgurate) tissue affected by genital warts. In many cases, local anesthesia is sufficient for patients undergoing this procedure.

Electrodesiccation. Although electrodesiccation is commonly used in the treatment of genital warts, few studies on this technique have been published. In one comparative study, electrodesiccation was found to result in a higher rate of complete wart clearance than podophyllin or cryotherapy (94% vs 41% and 79%, respectively).[11] All three treatment groups were found to have similar recurrence rates in the same range. Another advantage of electrodesiccation was the number of treatments required, a mean of 1.3 compared with >3 for the other two therapies.

Loop electrosurgical excisional procedure. Loop electrosurgical excisional procedure (LEEP) combines electroexcision and fulguration. In many clinics, it has replaced traditional electrosurgical techniques in the treatment of cervical intraepithelial neoplasia (CIN)[35] and external condylomata.[31] In the latter case, the lesion is elevated by a local anesthetic solution or saline (if the patient is treated under general anesthesia), and a small loop electrode is inserted into the superficial dermis (**Figure 1**).[30] This technique works best with larger, pointed warts; smaller, papular lesions are best treated by electrodesiccation.

A comparative study in >200 male and female patients found that the efficacy and adverse effects of LEEP are similar to those associated with laser ablation in the treatment of external condylomata.[31] Furthermore, LEEP resulted in less blood loss and a shorter operating time than did laser ablation or cold knife conization.[37]

Local anesthesia is typically given to patients with localized lesions, whereas those with extensive disease require general anesthesia. The most common side effect of LEEP for external anogenital condylomata is perioperative bleeding. If the loop electrode penetrates deep into the dermis, bleeding and scarring may result. Because scarring of the penis can result in dysfunction, most physicians prefer CO_2 laser vaporization or cryotherapy over LEEP for penile warts. Infections occur infrequently and can usually be controlled by antibiotics.

Surgical Excision

Surgical tangential excision using either cold knife or scissors has a high success rate in the treatment of genital warts, resulting in approximately 90% wart clearance rates and about 20% recurrence rates.[10,18] Although this technique is often reserved for extensive disease or refractory cases, surgical excision is also successful in the treatment of isolated warts. Compared with other physically ablative methods, surgical excision by a skilled physician is associated with good healing and less pain.

Interferons

Interferon (IFN) is an attractive candidate for the treatment of warts because it has immunomodulatory and antiproliferative effects as well as antiviral activity. Despite its antiviral effects, however, there is evidence that IFN therapy does not eradicate viral infection.[38]

To date, only IFN-α, the form of IFN produced by virus-infected leukocytes or lymphoblasts, is approved for intralesional use in the treatment of genital warts. Accordingly, most studies have been conducted with either natural or recombinant IFN-α. Various routes of IFN administration, including intralesional, topical, and parenteral, have been assessed in patients with genital warts (**Table II**).

Intralesional Therapy

Intralesional IFN treatment involves injections of the compound into the base of each wart. For recombinant IFN-α 2b (Intron A), injections are performed three times a week for 3 weeks, while for natural IFN-α (Alferon N), injections are performed two times a week for 8 weeks. For Intron, a maximum of five lesions can be treated at one session; the use of Alferon is limited by the total dose.

Controlled clinical trials have indicated that intralesional IFN therapy is more effective than placebo in clearing genital warts. In one study, 62% of pa-

TABLE II
Efficacy of Interferon in the Treatment of Genital Warts

Route of Administration	Clearance Rates (Range)	Recurrence Rates (Range)	References
Intralesional	36–53%	21–25%	[39–41]
Topical	33%	NR	[43]
Systemic	7–82%	23%	[8, 44, 45]

NR = Not reported.

Figure 1. The loop electrosurgical excisional procedure (LEEP).[36] Removal of external HPV lesion with the use of LEEP. (*A*) The skin around the lesion is stretched with the nondominant hand. (*B*) The loop is introduced superficially slightly into the dermis. (*C*) The lesion is removed by drawing the loop of the probe underneath the lesion and out on the other side.

tients treated with natural IFN-α had complete wart clearance, compared with 21% of placebo-treated patients.[39] Similarly, in a trial in which recombinant IFN-α was injected into single warts, a clearance rate of 53% was observed, compared with 14% for placebo-treated patients.[40] Another trial of recombinant IFN showed a lower incidence of complete clearance of IFN-treated warts (36% vs 17% for placebo) but found that the mean wart area decreased almost 40% from initial size in IFN-treated warts compared with an increase of 46% in warts treated with placebo.[41] Recurrence rates of approximately 20–25% have been reported in studies that included a follow-up assessment.[39,41]

Although intralesional IFN therapy helps to limit IFN's systemic effects, flulike symptoms are a common side effect of this treatment. Leukopenia may occur in patients treated for ≥3 weeks. In addition, intralesional administration is a time-consuming and painful procedure.

Topical Administration

Topical creams containing IFN avoid the need for intralesional injections and have minimal side effects.[42] Unfortunately, results obtained with topical IFN have been disappointing. In one clinical trial, the clearance rate in IFN-treated patients approximated 35% and was not significantly different from that re-

ported in the placebo group.[43] Thus, current preparations of topical IFN appear to offer little benefit in the treatment of genital warts.

Systemic Administration

Systemic administration of IFN is another option for selected rare patients with genital warts. In a study in which IFN gamma (IFN-γ) was administered intramuscularly to 28 patients with refractory condylomata acuminata, an overall response rate of 53% was observed.[44] In small studies involving daily subcutaneous or intramuscular injections of IFN-α or IFN-β, clearance rates of approximately 30% have been observed.[42] Recurrence rates have been encouragingly low in some studies,[45] but a larger trial found a recurrence rate of 28% and concluded that podophyllin treatment was significantly more effective than systemic IFN-α.[8]

The adverse effects associated with systemic IFN are substantial. In the small studies conducted to date, all patients experienced systemic adverse reactions.[42] Almost 30% of patients had to discontinue treatment due to adverse effects, and dose reductions were also common.

Adjuvant Therapy With IFN

There are some suggestions that IFN may be a valuable adjunct to conventional therapy, particularly in patients with refractory warts. Although subcutaneous IFN-α did not increase the efficacy of cryotherapy in one controlled trial,[46] another study indicated that prior systemic IFN-γ improved responses to cryotherapy.[44] Similarly, systemic IFN-α has been reported to lower the recurrence rate in patients treated with laser therapy.[47]

Adjuvant therapy with intralesional IFN has also been examined. One combination that has been studied is podophyllin and intralesional IFN.[9] Although adjunctive IFN resulted in a higher rate of complete clearance of warts (67% compared with 42% for podophyllin alone), recurrence rates were similar between the two groups (67% and 65%, respectively). More promising results were obtained when intralesional IFN was used as an adjuvant to either laser or 5-FU therapy. In this instance, a decreased incidence of recurrent anogenital lesions was found in patients who received adjuvant IFN therapy compared with those who did not (7% vs 24%).[48] An independent study of subcutaneous IFN therapy following CO_2 laser therapy found that clearance rates were twice as high in patients receiving adjuvant IFN therapy compared with those receiving placebo.[10]

NEW THERAPIES FOR THE TREATMENT OF EXTERNAL GENITAL WARTS

New therapies for genital warts focus on improving delivery of therapeutic agents to genital lesions and stimulating the immune system to combat the virus. These treatments offer exciting options to conventional treatments and may play an important role in future therapeutic decisions.

5-FU/Epinephrine

An injectable gel containing 5-FU and epinephrine in a protein carrier matrix of purified bovine collagen is being studied for use in the treatment of genital warts and some malignancies. The therapeutic compound in this formulation is 5-FU; epinephrine serves as a vasoconstrictor and acts to retain 5-FU at the site of the lesion.[50] This agent is thus able to maintain high local concentrations of 5-FU at the site of injection.

In a clinical trial of 401 patients with condylomata acuminata, patients received one intralesional treatment of 5-FU/epinephrine gel, 5-FU gel, or placebo per lesion once weekly for up to 6 weeks. A complete response rate of 61% occurred in the group receiving the 5-FU/epinephrine combination, compared with 43% in the group receiving 5-FU alone and 5% in the placebo group. Patients with limited disease (total lesion areas of $<100\ mm^2$) showed the best response to 5-FU/epinephrine, with a complete response rate of 71%; patients with more extensive lesions had a complete response rate of 25%. The 3-month recurrence rate in 5-FU/epinephrine-treated patients whose warts had regressed completely was 39%.[51]

Adverse effects of this therapy include pain during injection and local skin reactions, most notably erythema, swelling, erosions, and ulcerations. No systemic effects were observed in the clinical trial.

Solid-Formulation Podofilox

Gel and cream formulations of 0.5% podofilox have recently been tested for use in the treatment of external anogenital warts. Although the strength of podofilox is the same in the solid formulations as in the solution formulation currently available, the solid formulations are easier to apply and do not require an applicator. The treatment regimen involves application of solid-formulation podofilox twice daily for 3 consecutive days followed by a 4-day rest period. This treatment cycle is repeated until all warts are cleared or for a maximum of 8 weeks.

Although podofilox cream may be more convenient to apply than the solution formulation, its therapeutic efficacy does not appear to be improved. In a comparative study of podofilox cream versus podofilox solution in male patients with genital warts, similar clearance rates and side effects were observed in the two treatment groups.[52]

Podofilox gel has been compared to vehicle gel in a clinical trial, but there are as yet no published data from a comparative trial with podofilox solution. In

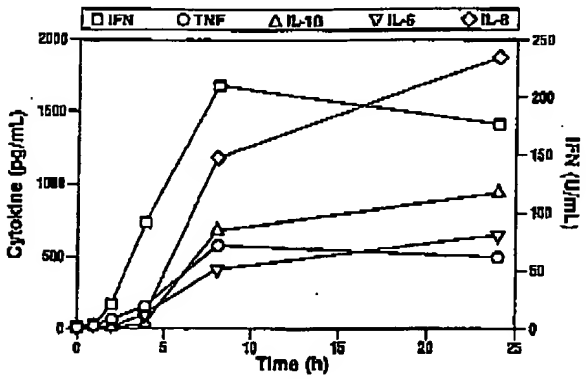

Figure 2. Kinetics of cytokine induction by imiquimod in human peripheral blood mononuclear cells. (Adapted from *J Leukoc Biol.*[57])

316 evaluable patients with anogenital warts, complete wart clearance was observed in 37% of 213 patients after four treatment cycles compared to 2% of 103 patients receiving vehicle gel.[53] After 8 weeks of treatment, 45% of podofilox-treated patients experienced complete wart clearance. Wart recurrence occurred in 32% of successfully treated patients, usually within the first 4 weeks following treatment.

These studies thus suggest that the efficacies of solid and solution formulations of podofilox are similar. However, the improved ease of application may make solid formulations of podofilox an attractive alternative to podofilox solution.

Imiquimod

One immune-response modifier that has recently become the focus of much study is imiquimod. Although imiquimod has no direct antiviral activity, preclinical studies in animal models have demonstrated that imiquimod is a potent inducer of IFN-α and enhances cell-mediated cytolytic activity against viral targets.[54,55] In cell-culture studies with human blood cells, imiquimod resulted in the production of high levels of IFN-α.[56] Imiquimod also induces a variety of other cytokines in human peripheral blood mononuclear cells, including interleukin-1 (IL-1), IL-6, IL-8, tumor necrosis factor (TNF), and IFN. The induction of cytokines is rapid and sustained (Figure 2).[57]

Imiquimod 5% cream has been tested in patients with genital warts in five multicenter, double-blind, vehicle-controlled, clinical trials. Patients applied the cream overnight (8 ± 2 hours) three times per week. Treatment was continued for up to 16 weeks or until warts were completely cleared. After a 12-week treatment-free period, the presence of warts was assessed.

Of the 209 patients enrolled in this trial, 109 patients received imiquimod 5% cream and 100 received vehicle cream. Of the 109 patients in the imiquimod 5% group, 36 completed 16 weeks of treatment without totally clearing their warts, 19 withdrew during the treatment period, and 54 totally cleared their warts. Of the 54 patients in the imiquimod 5% group who totally cleared their warts in the treatment period, 39 completed the 12-week follow-up period and remained clear. The other patients were either lost to follow-up or experienced recurrences (Figure 3).

Of the 100 patients in the vehicle group, 62 completed the 16 weeks of therapy without totally clearing their warts, 27 withdrew during the treatment period, and 11 totally cleared their warts. Of the 11 patients in the vehicle group who totally cleared their warts in the treatment period, 9 completed the 12-week follow-up period and remained clear. The other patients were either lost to follow-up or experienced recurrences (Figure 3).

The patients treated with imiquimod 5% cream had clearance rates of 50% (72% of females, 33% of males), which were significantly higher than those in patients receiving vehicle cream, who had total clearance rates of 11% (20% of females, 5% of males).[58]

Higher clearance rates were observed in females than in males, possibly due to differences in keratinization of wart tissue.

Local skin reactions, including erythema (61%), erosion (30%), and excoriation/flaking (23%), were the most commonly reported treatment-related events. These reactions were usually mild to moderate in intensity. Overall, 1.2% (4/327) of the patients discontinued due to local skin/application-site reactions.[58]

These data suggest that topical imiquimod may have several advantages over conventional agents in the treatment of external genital warts. Imiquimod is easily applied by the patient and results in acceptable total clearance rates. Systemic side effects are negligible, and local effects are generally tolerable. Topical administration of imiquimod may thus be a suitable therapeutic choice for first-line treatment of external genital warts.

PROSPECTS FOR A VACCINE

As a viral disease, HPV infection is a candidate for preventative vaccination.[54] A successful vaccine could potentially reduce the number of cases of HPV-associated genital cancers, particularly cervical malignancies. Current efforts are targeted at the development of prophylactic vaccines to prevent HPV disease and therapeutic vaccines that help boost the host's immune response to HPV-infected cells.

Because HPV cannot be cultured, most attention to date has been focused on the possibility of a vaccine composed of a specific HPV subunit. Such a

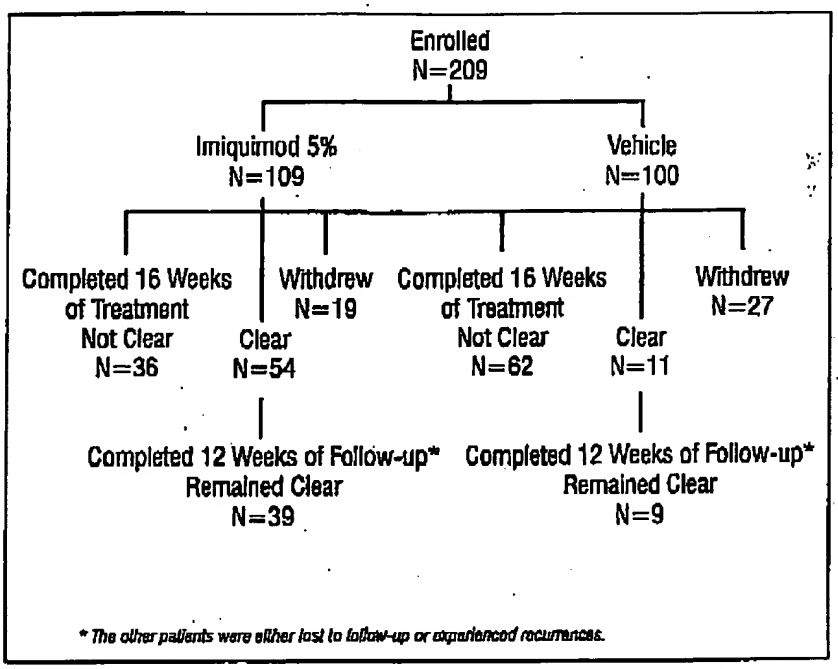

Figure 3. Imiquimod patient accountability for Study 1004 clinical trial.[58]

strategy has been successfully employed in the development of a vaccine for the hepatitis B virus. Potential candidates for an immunogenic HPV subunit include the major and minor capsid proteins L1 and L2. L1, by itself or with L2, can self-assemble into virus-like particles that have a conformation similar to that of intact virions.[60,60] In animal model systems, immunization with these virus-like particles results in the production of antibodies capable of neutralizing the intact virus.[61,62] Alternatively, peptides from the E6 or E7 proteins—the HPV-transforming proteins—are a possible source of a prophylactic or therapeutic vaccine against HPV-associated malignancies.[61]

A potential difficulty with vaccines for genital warts is that >20 different types of HPV can cause genital lesions.[63] Accordingly, effective vaccination will require either the identification of a common antigenic epitope or the development of a multivalent vaccine directed against the relevant HPV types.

CONCLUSIONS

A variety of therapies are available for the treatment of genital warts. The best choice of treatment for a given patient depends on the extent and location of disease and the preferences of the clinician and patient.

Current therapies for the treatment of genital warts probably do not eradicate the viral reservoir present in adjacent tissue. Thus, in many cases these treatments are destined to fail, as indicated by the high rate of recurrent infections. Despite the high recurrence rates associated with current therapies, however, wart clearance is usually achieved in the majority of patients. In some cases, several therapies must be tried over a period of a few months to a year. Even when warts do recur, the patients receive some benefit from a sustained wart-free period.

There is little doubt, however, that new therapeutic options would be a welcome addition to the arsenal of treatment modalities available for genital warts. By prompting the host to join the fight against HPV infection, new immunomodulatory therapies and vaccines hold promise for increasing the success rate of treating genital warts. Improving the delivery of therapeutic compounds to the site of infection may also produce beneficial results.

None of the therapies studied to date purports to be a "cure" for HPV infection. However, with every advance in the treatment of genital warts, more is learned about this disease and the optimal method of combating it. Most importantly, these advances may translate into reduced pain and discomfort for patients with genital warts.

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63. de Villiers E-M. Heterogeneity of the human papillomavirus group. *J Virol.* 1989;63:4898–4903.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Audrey Goddard et al.	Examiner:	Lorraine Spector
Serial No.:	09/202,054	Group Art Unit:	1647
Filed:	December 7, 1998	Docket:	G&C 669.23-US-WO
Title:	HUMAN TOLL HOMOLOGUES		

DECLARATION OF J. FERNANDO BAZAN UNDER 37 C.F.R. § 1.132

I, J. FERNANDO BAZAN, declare as follows:

1. I am currently employed as a Senior Scientist at Genentech, Inc. Prior to my employment at Genentech, Inc., I was employed at DNAX Research Institute. I hold a Ph.D. in Biophysics and have been working in the field of technology relating to Toll proteins for over 10 years. A copy of my Curriculum vitae is included herein as Attachment A.

2. I understand that the above-referenced patent application was filed by Genentech, Inc. on December 7, 1998 ("the '054 application"). I was provided a copy of the '054 application by Genentech's patent attorney, and I have reviewed the '054 application.

3. The '054 application describes that a BLAST and FastA sequence alignment analysis showed that the polypeptide referred to as PRO285 is a human analogue of the Drosophila Toll protein, and is homologous to cytoplasmic domains of human interleukin 1 receptor and the following human Toll proteins: Toll1 (DNAX# HSU88540_1), Toll2 (DNAX# HSU88878_1), Toll3 (DNAX# HSU88879_1), and Toll4 (DNAX# HSU88880_1)". See, e.g. Figure 7B and page 40, lines 19-23, of the '054 application.

4. The '054 application also describes that specific regions of PRO285 homology include a 13 residue intracellular segment that is associated with NF-κB activation in Toll-like receptor 2 and Interleukin-1 receptor (as shown in Figure 7B and described at page 7, lines 8-23, of the '054 application). A sequence alignment showing this region of homology in the Interleukin-1 receptor, the Toll-like receptor 2 and PRO285 is provided herein as Attachment B. As shown in Attachment B, 9 of

the 13 residues in this region of PRO285 are either identical to or are conservative amino acid substitutions of the corresponding residues in the Interleukin-1 receptor and/or Toll-like receptor 2.

5. The '054 application describes that that 13 amino acid region is crucial for receptor mediated signaling and NF-κB activation in both the interleukin-1 receptor and the Toll-like receptor 2. At page 7, lines 8-23, the '054 application states that this C-terminal region in the Interleukin-1 receptor contains residues essential for IL-1R signaling. At page 7, lines 8-23 and in Example 11, the '054 application states that when this 13 amino acid C-terminal region in the Toll-like receptor 2 polypeptide is deleted, the resulting truncated variant can no longer induce NF-κB activation.

6. Prior to and at the time of the filing of the '054 application, I was working in the field of technology relating to Toll proteins at the DNAX Research Institute in Palo Alto, CA. I am a principal author of the article entitled "A Family of Human Receptors Structurally Related to *Drosophila* Toll" published in 1998 in the Proceedings of the National Academy of Sciences, Volume 85, pages 588-593. I note that this article was cited by Genentech in the '054 application. See, e.g. '054 application at page 2, line 25.

7. In the article referred to in Paragraph 6 above, I and my co-authors teach that given the sequence homology between the cytoplasmic domains of Toll polypeptides and the cytoplasmic domains of human interleukin 1 receptors, it is expected that both molecules trigger signaling pathways tied to Rel-type transcription factors such as NF-κB. See, e.g. page 588. The article further teaches that, as suggested from sequence homology data, Toll-like receptor 4 activates NF-κB and triggers the production of several inflammatory cytokines, hallmarks of an innate immune response. See the note at page 593 which describes the disclosure of Medzhitov et al., Nature 388, 394-397 (1997).

8. I believe that based on at least the description in the '054 application, the sequence homology data relating to PRO258, and the state of the art, one skilled in the art would reasonably understand that PRO285 can induce the activation of NF-κB and/or the expression of NF-κB-controlled genes and that antibodies to PRO285 could be made and used in accordance with routine techniques to modulate such activity.

9. I further declare that all statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: December 1, 2003

J. FERNANDO BAZAN, Ph.D.

DECLARATION
ATTACHMENT A

Curriculum Vitae

JOSE FERNANDO BAZAN, PH.D.

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Palo Alto, CA 94301-1727
USA

tel 650.321.9436
cell 650.224.0686
email jfbazan@proteinmachines.org
web www.proteinmachines.org

Personal

U.S. Citizen
Fluent in English and Spanish

Education

Ph.D. in Biophysics, December 1989
University of California, Berkeley

thesis Structural, evolutionary and crystallographic studies of growth factors, viral proteases and bifunctional enzymes (Advisors: Tom Jukes, UCB, and Robert Fletterick, UCSF)

B.S. in Physics, June 1982
Stanford University

thesis e+/e- collisions on the SPEAR ring at SLAC (Advisor: Alan Litke)

Professional

DNAX Research Institute (1993-2002)

Senior Staff Scientist, Dept. of Genomics (Mar. 1998-Nov. 2002)

Functional and comparative genomics, proteomics, molecular immunology, receptor mechanisms of signal transduction, receptor/ligand matching, protein structure & design, drug discovery & development, *in vivo* animal models, inflammatory and autoimmune diseases

Staff Scientist, Dept. of Molecular Biology (Dec. 1994-Feb. 1998)

Structural and computational biology, novel immune factor discovery, molecular recognition in receptor/ligand engagements, protein engineering, innate immune receptors (TLRs)

Visiting Fellow, Frank Lee lab, Dept. of Molecular Biology (Oct. 1993-Dec. 1994)

Cytokine structural biology, ADP Ribosyltransferases, novel factor discovery, protein structure prediction & modeling

Accomplishments

- Formed and led an innovative and very successful laboratory that was engaged in the discovery and characterization of novel proteins involved in critical immune regulatory pathways, weaving together state-of-the-art bioinformatics, biophysical and cellular methods with functional genomic and proteomic tools.

- Predicted an unusual enzymatic activity for CD38, confirmed by experiment. Sparked research into ADP-ribosyltransferases, finding a large family of human enzymes whose biological functions continue to be explored in collaboration with other investigators.
- Critically helped identify the cytokine ligand for the Flt-3 receptor by seeking a sequence fragment suggesting a predicted fold & receptor similiarity with stem cell factor and M-CSF. This has been recently confirmed by crystallographic studies.
- Played a leading role in the discovery, characterization and receptor matching of a number of novel IL-1-like, IL-17-like, TNF/C1Q-family, and hemopoietic (NNT-1, TSLP, IL-10-like, IL-23, IL-27, IL-28-like) cytokines.
- First to identify and clone the full complement of human and mouse Toll-like receptors (TLRs) that are now under intense study as critical innate immune receptors.
- Initiated efforts to develop novel molecules (such as TSLP, IL-23 and IL-27) and specific monoclonal antibodies as therapeutic entities for the treatment of a variety of human immune disorders.
- Guided the design and implementation (with Beth Basham) of web-accessible databases that catalogued and linked together in-house protein projects (sequences, cDNAs, structural & prediction data, antibodies, purified protein stock, etc.) with external sites (NCBI, PubMed, Interpro, various microarray data depositories) and tools (sequence comparison, fold recognition, transmembrane & signal peptide prediction, genomic).
- Pioneered (in collaboration with R. Kastelein & D. Gorman research groups) an integrated, systems-based approach to molecular analysis at DNAX. This multidisciplinary approach partly comprised:
  - (i) Utilizing sensitive computational & structure-based tools to discover fold relatives in broad genomic databases
  - (ii) Developing the facility to rapidly clone and characterize the relevant families of (putatively) expressed genes, and capturing their chromosomal loci for subsequent gene deletion projects
  - (iii) Using EST spread, microarray and Taqman-generated data to derive comparative expression profiles of genes of interest
  - (iv) Expressing proteins (or predicted domain fragments) in a variety of systems (bacterial, yeast, insect cell, mammalian cell) typically by retroviral or adenoviral infection
  - (v) Emphasizing biochemical tools (such as circular dichroism, calorimetry) to purify, analyze and confirm the predicted structures & activities of proteins
  - (vi) Using structural models for protein engineerin, such as in the design of cytokine antagonists.
  - (vii) Speeding drug design by employing X-ray and NMR techniques to elucidate the structure of compelling molecules in collaborations with groups at Stanford and Berkeley,
  - (viii) Performing biophysical (like Biacore) and genetic studies to discern & catalogue the complex interactions of families of interacting ligands and receptors
  - (ix) Guiding novel proteins through an array of *in vitro* and *in vivo* experiments (from cell-based to animal disease models) to validate their use in clinical applications

Current research

- Novel hemopoietic cytokines that regulate the differentiation of naïve T cells into Th1 and Th2 developmental subtypes
- Mechanisms of innate *vs.* adaptive immunity—primitive defense factors and receptors that trigger cytokine pathways
- Utilizing comparative genomics approaches to map the emergence of the various superfamilies (organized by fold class) of immune regulators across the spectrum of completed genomes
- Designing a web site (linked to www.proteinmachines.org) to publish a complete structural taxonomy—from either determined or accurately modeled proteins—of cytokines and their receptors, with a focus on molecular recognition and signaling facets
- Capturing novel peptide and small molecule antagonists of cytokine receptor signaling by targeting novel fold intermediates
- Genetic basis and molecular mechanisms of complex human diseases (with particular interest in type I diabetes and other autoimmune & inflammatory disorders).

University of California, San Francisco (1985-1993)

Postdoctoral Fellow (Oct. 1991-Oct. 1993)
Structural biology: protein and drug design
Dept. of Biochemistry & Biophysics, Program of Excellence, Cardiovascular Research Institute
Robert J. Fletterick & Lewis T. Williams, Principal Investigators.

Postdoctoral Fellow, Oct. 1989-Oct. 1991
Molecular evolution of protein structure (Alfred P. Sloan Fellowship)
Department of Biochemistry & Biophysics
Robert J. Fletterick, Principal Investigator.

- Early involvement in the application of novel 2^0 and 3^0 structure prediction, fold recognition and modeling techniques (exploiting evolutionary information inherent in families of distant sequences) to successfully predict the structures and biochemical functions of proteins.
- Discovered and characterized a novel family of viral proteases essential for picorna & flavivirus maturation whose predicted folds and activities have been confirmed by X-ray studies and are active targets of drug design efforts.
- First defined & categorized the conserved structural architectures of various superfamilies of cytokines & their receptors (notably hemopoietic) with a focus on their modes of engagement, and mechanisms of specificity & signal transduction. These predictions have been validated by structural work, and laid the foundation for a broad genomics-based effort to identify novel molecules by fold recognition methods.
- Argued successfully that a published crystal structure of IL-2 was incorrectly traced, and modeled an alternative fold that agreed better with experimental data.
- Trained in experimental X-ray crystallography and biochemistry (Fletterick lab), evolutionary molecular biology (Jukes lab), computational biology (Fred Cohen lab), and immunology (Williams lab), the latter work introducing me to DNAX, a preeminent immunological institute.

Stanford University (1978-1982)

Research Assistant, 1987-89
Depts. of Pharm. Chemistry, and Biochemistry & Biophysics
Structural biology and targeted drug design for AIDS (NIH study)
George Kenyon, Director.

Research Assistant, 1987-88
Dept. of Neurology, School of Medicine
Prion structural biology (NIH Trainee)
Stanley Prusiner, Principal Investigator.

Research Technician, 1980-81
Senior thesis research: Experimental high-energy particle physics at the Stanford Linear Accelerator
Department of Physics, Stanford University
Alan Litke, Principal Invesigator.

Research Technician, 1979
Department of Physics, Stanford University
Stuart Freedman, Principal Investigator.

Teaching

Recurring lectures in Molecular Immunology, 2001-present
(Structure & Evolution of Cytokine Receptors; Signaling Mechanisms of Innate Immune Pathways)
Advanced Immunology 211/212 graduate courses, K.C. Garcia (organizer), Stanford University

Teaching Assistant, 1983-1985
Physics 7A-C: Introductory physics for scientists &engineers (with laboratory)
Department of Physics, University of California, Berkeley
- Head T.A., 1983 (Oversaw the quality of teaching of over 20 T.A.'s, conducted large review lectures, organized exam and homework grading)

Teaching Assistant, 1980-82
Physics 51-58: Mechanics, electricity & magnetism and modern physics (with laboratory)
Department of Physics, Stanford University
- Head T.A., 1981 (Coordinated T.A.'s in lab and lecture duties, exam and paper grading)

Mentoring

Graduate students & Postdoctoral fellows (with Current Positions)

Jorge Guimarães, M.D., Ph.D., 1995-1997
(Faculty & clinical post at the Univ. of Oporto Medical School, Portugal)

Fernando L. Rock, Ph.D., 1994-1997
(Staff Scientist, PPD Discovery, Menlo Park)

Gary Hardiman, Ph.D., 1994-1997
(Director of the Biomedical Genomics Microarray Facility at UC. San Diego)

Sriram Balasubramanian, Ph.D., 1995-1996 (with Gerard Zurawski)
(Senior Staff Scientist at Axys Pharmaceuticals/Celera, South San Francisco)

Theo Sana, Ph.D., 1995-1999 (with Rob Kastelein)
(Staff Scientist, Agilent, Palo Alto)

Frederich Koch-Nolte, M.D., 1994, and 1997
(Faculty position at the University Clinic, Hamburg)

Birgit Oppmann, Ph.D., 1997-2000 (with Rob Kastelein)
(Max-Delbruck-Zentrum fur Molekulare Medizin, Berlin)

Reno Debets, Ph.D., 1997-2000 (with Rob Kastelein)
(Faculty position, Dept. of Medical Oncology, Erasmus Medical Center & the Daniel den Hoed Clinic, Rotterdam)

Beth Basham, Ph.D., 1998-2000
(Staff Scientist, DNAX Research Institute, Palo Alto)

Pedro Reche, Ph.D., 1998-2001
(Principal Investigator, Molecular Immunology Foundation, Dana Farber Cancer Institute, Harvard Medical School)

Stefan Pflanz, Ph.D., 1999-2002 (with Rob Kastelein)
(Staff Scientist, Micromet, Munich)

Joao Pereira, 2001-2002
(Ph.D. Graduate student, Pasteur Institute, Paris)

Peter Kirk, Ph.D., 2000-present

Jochen Schmitz, Ph.D., 2001-present

Alexander Owyang, Ph.D., 2002-present

Honors

Alfred P. Sloan Foundation Fellow in Studies of Molecular Evolution, 1990-91

University Fellowship, 1985-87, University of California, Berkeley.

Rebecca Carrington Award, June 1982, to a graduating senior in Physics, Stanford University.

President, Society of Physics Students, 1980-81, Stanford University.

Patents

Author on over 45 patent applications relating to the discovery and therapeutic application of novel molecules; a dozen of these have been granted in the U.S. as of Dec. 2002.

Societies

AAAI, AAAS, American Crystallographic Association, The Cytokine Society, The Protein Society

Publications

In preparation or submitted

Schmitz, J., **Bazan, J. F.** (2003) A long LOST cytokine is found. *Trends Immunol.* In preparation.

Kirk, P., **Bazan, J. F.** (2003) IL-17 receptors explained. *In preparation.*

Bazan, J. F., Kastelein, R. A. (2003) The control of Th1 development by the IL-27, IL-12 and IL-23 axis of cytokines. *Ann. Rev. Immunol.*, in preparation.

Bazan, J. F. (2003) Structure and evolution define the interactions and signaling mechanisms of hemopoietic cytokines and their receptors. *Adv. Prot. Chem.*, in preparation.

Reche, P., **Bazan, J. F.** (2003) Symmetry and function in death domain fold architecture. *J. Molec. Biol.*, in preparation.

Bazan, J. F. (2003) Origins of the hematopoietic cytokine helical fold. *J. Molec. Biol.*, in preparation.

Owyang, A., **Bazan, J. F.** (2002) An evolutionary intermediate in the divergence of IL-10 and IFN-α/β families of cytokines. *Trends Immunol.*, in preparation.

Bazan, J. F. (2002) Invertebrate helical cytokines. *Curr. Biol.*, submitted.

Bazan, J. F. (2002) Predicted membrane topology and globular architecture of Wolframin, a complex transmembrane protein implicated in Wolfram's Syndrome. *Proteins*, submitted.

Kirk, P., Pereira, J., **Bazan, J. F.** (2002) A genomic perspective on the TLR signaling pathway. *Genome Res.*, submitted.

Bazan, J. F. (2002) Receptor complexes: a paradigm revisted. *Nature Struct. Biol.*, submitted.

Boonstra, A., Crain, C., Liu, Y.-J., Pereira, J., Kastelein, R. A., **Bazan, J. F.**, de Waal-Malefyt, R., Vieira, P., O'Garra, A. (2002) Differential expression of Toll-like receptors on mouse dendritic cell subsets: expression profile and functional consequences. *J. Exp. Med.*, submitted.

Refereed journal articles

Hibbert, L., Pflanz, S., Vaisberg, E., Rosales, R., **Bazan, J. F.**, de Waal-Malefyt, R., Kastelein, R. A. (2002) IL-27 and IFNα induce T-bet and IL-12Rβ2 in naïve T-cells. *Nature Immunol.*, in press.

Bazan, J. F. (2002) Evolution of TLR signaling mechanisms. *Biochem. Soc. Trans.*, in press.

Glowacki G., Braren, R., Firner, K., Nissen, M., Kuhl, M., Reche, P., **Bazan, J. F.**, Cetkovic-Cvrlje, M., Leiter. E., Haag, F., Koch-Nolte, F. (2002) The family of toxin-related ecto-ADP-ribosyltransferases in humans and the mouse. *Protein Sci.* 11, 1657-1670.

Koch-Nolte, F., Reche, P., Haag, F., **Bazan, J. F.** (2001) ADP- ribosyltransferases: plastic tools for inactivating protein and small molecular weight targets. *J. Biotechnol.* 92, 81-87.

Pflanz, S., Timans, J. C., Cheung, J., Rosales, R., Kanzler, H., Gilbert, J., Hibbert, L., Churakova, T., Travis, M., Vaisberg, E., Blumenschein, W. M., Mattson, J. D., Wagner, J. L., To, W., Zurawski, S., McClanahan, T. K., Gorman, D. M., **Bazan, J. F.**, de Waal-Malefyt, R., Rennick, D., Kastelein, R. A. (2002) IL-27, a heterodimeric cytokine composed of EBI3 and p28 protein, induces proliferation of naive CD4(+) T cells. *Immunity* 16, 779-790.

Soumelis, V., Reche, P. A., Kanzler, H., Yuan, W., Edward, G., Homey, B., Gilliet, M., Ho, S., Antonenko, S., Lauerma, A., Smith, K., Gorman, D., Zurawski, S., Abrams, J., Menon, S., McClanahan, T., de Waal-Malefyt, R., **Bazan, J. F.**, Kastelein, R. A., Liu, Y.-J. (2002) Human epithelial cells trigger dendritic cell mediated allergic inflammation by producing TSLP. *Nature Immun.* 3, 673-680.

Sims, J., Nicklin, M. J., **Bazan, J. F.**, Barton, J. L., Busfield, S. J., Ford, J. E., Kastelein, R. A., Kumar, S., Lin, H., Mulero, J., Pan, J. G., Pan, Y., Smith, D. E., Young, P. R. (2001) A new nomenclature for IL-1 family genes. *Trends Immunol. 22,* 536-537.

Kadowaki, N., Ho, S., Antonenko, S., de Waal-Malefyt, R., Kastelein, R. A., **Bazan, J. F.**, Liu, Y.-J. (2001) Subsets of human dendritic cell precursors express different Toll-like receptors and respond to different microbial antigens. *J. Exp. Med 194,* 863-870.

Neighbors, M., Xu, X., Barrat, F. J., Ruuls, S. R., Churakova, T., Debets, R., **Bazan, J. F.**, Kastelein, R. A., Abrams, J. S., O'Garra, A. (2001) A critical role for interleukin 18 in primary and memory effector responses *to Listeria monocytogenes* that extends beyond its effects on interferon-γ production. *J. Exp. Med 194,* 343-354.

Reche, P. A., Soumelis, V., Gorman, D. M., Clifford, T., Liu, M.-R., Travis, M., Zurawski, S. M., Johnston, J., Liu, Y.-J., Spits, H., de Waal-Malefyt, R., Kastelein, R. A., **Bazan, J. F.** (2001) Human thymic stromal lymphopoietin preferentially stimulates myeloid cells. *J. Immunol.* 167, 336-343.

Loughced, J. C., Holton, J. M., Alber, T., **Bazan, J. F.**, Handel, T. M. (2001) Structure of melanoma inhibitory activity protein, a member of a recently identified family of secreted proteins. *Proc Natl Acad Sci U. S. A.* 98, 5515-20.

Fahrer, A. M., **Bazan, J. F.**, Papathanasiou, P., Nelms, K. A., Goodnow, C. C. (2001) A genomic view of immunology. *Nature* 409, 836-838.

Debets, R, Timans, J. C., Churakowa, T., Zurawski, S., de Waal-Malefyt, R., Moore, K. W., Abrams, J. S., O'Garra. A., **Bazan, J. F.**, Kastelein, R. A. (2000)IL-18 receptors, their role in ligand binding and function: anti-IL-1RAcPL antibody, a potent antagonist of IL-18. *J. Immunol.* 165, 4950-4956.

Taylor, K. R., Holzer, A. K., **Bazan, J. F.**, Walsh, C. A., Gleeson, J. G. (2000). Patient mutations in doublecortin define a repeated tubulin-binding domain. *J. Biol Chem.* 275, 34442-34450.

Sana, T. R., Debets, R., Timans, J. C., **Bazan, J. F.**, Kastelein, R. A. (2000) Computational identification, cloning, and characterization of IL-1R9, a novel interleukin-1 receptor-like gene encoded over an unusually large interval of human chromosome Xq22.2-q22.3. *Genomics* 15, 252-262.

Oppmann, B., Lesley, R., Blom, B., Timans, J.C., Xu, Y., Hunte, B., Vega, F., Yu, N., Singh, K., Zonin, F., Vaisberg, E., Churakova, T., Liu, M.-R., Gorman, D.M., Wagner, J., Zurawski, S., Liu, Y.-J., Abrams, J.S., Moore, K.W., de Waal-Malefyt, R., Hannum, C., Rennick, D., **Bazan, J. F.**, Kastelein, R.A. (2000) Novel p19 protein engages IL-12 p40 to form a cytokine, IL-23, with biological activities similar as well as distinct from IL-12. *Immunity* 13, 715-725.

Wiekowski, M., Leach, M., Evans, E., Sullivan, L, Chen, S.-C., **Bazan, J. F.**, Gorman, D.M., Kastelein, R.A., Narula, S. Lira, S.A. (2001) Ubiquitous transgenic expression of the IL-23 subunit p19 induces multiorgan inflammation, runting, infertility, and premature death. *J. Immunol.* 166, 7563-7570.

Pan, S., Tsuruta, R., Masuda, E. S., Imamura, R., **Bazan, J. F.**, Arai, K., Arai, N., Miyatake, S. (2000) NFATz: a novel Rel similarity domain containing protein. *Biochem Biophys Res Commun.* 272, 765-776.

Debets, R., Timans, J. C., Homey, B., Zurawski, S., Sana, T. R., Lo, S., Wagner, J., Edwards, G., Clifford, T., Menon, S., **Bazan, J. F.**, Kastelein, R. A. (2001) Two novel IL-1 family members, IL-1δ and IL-1ε, function as an antagonist and agonist of NF-κB activation through the orphan IL-1R related protein 2. *J. Immunol.* 167, 1440-1446.

Patel, N., Brinkman-Van der Linden, E. C., Altmann, S. W., Gish, K., Balasubramanian, S., Timans, J. C., Peterson, D., Bell, M. P., **Bazan, J. F.**, Varki, A., Kastelein, R. A. (1999) OB-BP1/Siglec-6. a leptin- and sialic acid-binding protein of the immunoglobulin superfamily. *J. Biol. Chem.* 274, 22729-22738.

Rossi, D. L., Hardiman, G., Copeland, N. G., Gilbert, D. J., Jenkins, N., Zlotnik, A., **Bazan, J. F.** (1999) Cloning and characterization of a new type of mouse chemokine. *Genomics* 47, 163-170

Mizoue, L. S. , **Bazan, J. F.**, Handel, T. M. (1999). Solution structure and dynamics of the chemokine domain of fractalkine and its interaction with an N-terminal fragment of CX3CR1. *Biochemistry* 38, 1402-1414.

Cacalano, N. A., Migone, T. S., **Bazan, J. F.**, Hanson, E. P., Chen, M., Candotti, F., O'Shea, J. J., Johnston, J. A. (1999) Autosomal SCID caused by a point mutation in the N-terminus of Jak3: mapping of the Jak3-receptor interaction domain. *EMBO J* 18, 1549-1558.

Rock, F. L., Hardiman, G., Timans, J. C., Kastelein, R. A., **Bazan, J. F.** (1998). A family of human receptors structurally related to *Drosophila* Toll. *Proc. Natl. Acad. Sci. USA* 95, 588-593.

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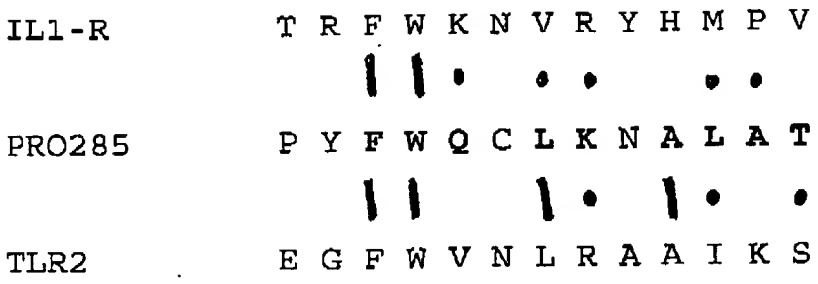
Talks

Cold Spring Harbor meeting on *Viral Proteinases as Targets for Chemotherapy*, May 1989 (invited speaker).

Int. Soc. Interferon Res. Annual Meeting in San Francisco, Nov. 1990 (invited speaker).

DECLARATION
ATTACHMENT B



• Indicates amino acids having conserved side chain properties.

RELATED PROCEEDINGS APPENDIX

NONE